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On Sept. 24, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: [signature]

PATENT
Attorney Docket No.: 016252-002110US

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Laurie A. Graham et al.

Application No.: 10/032,658

Filed: November 8, 2001

For: TENEBRIO ANTIFREEZE PROTEINS

Examiner: Ramirez, Delia M.

Art Unit: 1652

RECONSIDERATION OF REQUIREMENT PURSUANT TO RULE 143

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Communication is in response to a Restriction Requirement mailed on July 26, 2002, requiring an election of claims. A petition for an extension of the time period for response of one month until September 26, 2002, is enclosed.

PROVISIONAL ELECTION

Pursuant to Rule 143, Applicants *provisionally* elect Group I, claims 36-49 and 78-81 drawn in part to antifreeze protein Seq. ID No. 11.

ARGUMENT

Applicants respectfully disagree with the restriction of their invention into six groups. Reconsideration of the restriction requirement is requested pursuant to Rule 143. The following reasons are submitted as a basis for considering all six groups as a single invention. The inventions are not independent and distinct inventions. There is a linking claim that defines the proteins as a single group with similar functional and structural properties. There is no undue burden on the Examiner to examine the group as defined by the claims. The MPEP specifically permits the PTO to examine up to 10 sequences in a single application where the sequences are patentably indistinct.

a. The invention.

This invention is the discovery of a family of insect anti-freeze proteins defined by a signature sequence set forth in SEQ ID NO: 3. Four different isoforms are described. The pending claims represent a divisional from an issued application US Pat. No. 6,392,024 with claims to nucleic acids encoding the proteins incorporating the isoforms.

b. The restriction requirement.

The Examiner has restricted the pending claims 36-81 into six groups. Group I includes the linking claims 36 and 78 and YL-1 (isoform #1). Groups II-IV are identical but each includes a different isoform YL-2 and YL-4.

Group V is drawn to claims 50-63 which generically claim the novel isoform family by its biological properties and by it being encoded by a nucleic acid that specifically binds to a conserved signature sequence set forth in SEQ ID NO:2.

Group VI is drawn to claims 64-77 which generically describe a family of insect antifreeze protein isoforms that are encoded by nucleic acids that bind under stringent hybridization conditions to SEQ ID NO:12 which is YL-2.

c. The restriction requirement is improper because there is no undue burden on the Examiner to search and determine if the four isoforms are novel.

The MPEP 803.01 requires the examiner to determine that the claims embrace independent and distinct inventions and that there be an undue burden to examine all the inventions in a single application. Neither test is met here.

The four isoforms *per se,* and the family defined by the claims including Groups V and VI, are not distinct and independent inventions. The pending claims are not an arbitrary collection of sequences submitted by applicants that use "brute force" sequencing methods. The family of antifreeze isoforms defined by the claims are evolutionarily related. They are defined structurally by a conserved N-terminus motif, SEQ ID NO: 3. They have both structural and functional similarities that are the basis for their being grouped as a family of isoforms.

There is no undue burden on the Examiner to search the claimed antifreeze protein family. The claims define a readily apparent search strategy that is well defined and narrow in scope. Either the isoforms *per se*, or the motif, can be searched in a rapid and conventional manner to determine if the proteins are novel. Further evidence of a lack of undue burden can be found in the file history of the parent application. The subject application is a divisional of an issued patent, US Pat. No. 6,392,024 ['024] in which the prior examiner had no problem searching nucleic acids encoding all four isoforms. A copy of the issued claims is attached for the convenience of the Examiner.

In addition to the first four groups, the examiner of the '024 patent kept the equivalents of Groups V and VI with the other groups together. Issued claims 6 and 7 of the '024 patent correspond to independent claims 50 and 64 of the subject application.

d. The PTO expressly recognized circumstances such as those presented by the pending claims in MPEP 803.04.

The MPEP 803.04 expressly submits that the PTO will search at least 10 nucleotide sequences per application and it will only be in exceptional circumstances that less than 10 nucleotide sequences will be examined. The MPEP states:

> In some exceptional cases, the complex nature of the claimed material, for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than ten.

The subject claims do not present extraordinary circumstances. The claims recite standard combinations of physical and functional elements that sufficiently limit the claims to the family of antifreeze protein isoforms both naturally occurring and man made.

Finally, applicants would note that a mechanical determination that any two proteins are independent and distinct is erroneous. The MPEP notes that this is a rebuttable position. Applicants have already explained that the isoforms described herein are related proteins by both function and structure.

Based upon the above remarks, applicants submit that claims 36-81 represent a single invention and the claims should be rejoined.

Should the Examiner believe that a telephone interview would expedite prosecution in any way, she is invited to call the undersigned attorney at the number provided.

Respectfully submitted,

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Enclosures: Issued claims of parent Pat. 6,392,024
Petition for Extension of Time (1 mth.)

SF 1384866 v1

-continued

lambda-Zap cDNA library"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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CACTGCACTG GGGGTGCTGA TTGTACTAGT TGTACAGATG CATGCACTGG TTGTGGAAAT     60

TGTCCAAATG CACATACGTG TACCGATTCC AAAAATTGTG TCAAGGCAGC AACATGTACT    120

GGATCTACAA AATGTAATAC CGCCAGGACG TGTACAAACT CAAAAGACTG TTTTGAAGCC    180

AAAACATGTA CTGACTCAAC CAACTGTTAC AAAGCTACAG CCTGTACCAA TTCAACAGGA    240

TGTCCCGGAC ATTAAGTTTT TCTATTGTCA ACAATAATAA AACACACTTA CTGTTATCTT    300

AGCTAAAACA TAA                                                       313
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(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa
1               5                   10                  15

Cys Xaa Xaa Cys
            20
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What is claimed is:

1. An isolated nucleic acid encoding an antifreeze protein, said protein defined as follows:

(i) having a calculated molecular weight of between 7 and 13 kDa;

(ii) having a thermal hysteresis activity greater than 1.5° C. at about 1 mg/mL;

(iii) having a nucleic acid subsequence which encodes the N-terminal motif set forth in Seq. ID No. 3;

(iv) specifically binding to polyclonal antibodies raised against antifreeze protein selected from the group consisting of YL-1, YL-2, YL-3 or YL-4: and,

(v) having at least about 70% amino acid sequence identity to an antifreeze protein selected from the group consisting of YL-1, YL-2, YL-3 or YL-4.

2. The isolated nucleic acid of claim 1, wherein the calculated molecular weight of the encoded protein is between about 8 and 12 kDa.

3. The isolated nucleic acid of claim 1, wherein the thermal hysteresis activity is greater than 2° C. at 1 mg/mL.

4. The isolated nucleic acid of claim 1, wherein the encoded protein includes a subsequence of amino acids corresponding to Seq ID No: 4.

5. The isolated nucleic acid of claim 1 selected from the group consisting of: YL-1 (SEQ ID NO. 10), YL-2 (SEQ ID NO. 12), YL-3 (SEQ ID NO. 16) and YL-4 (SEQ ID NO. 14).

6. An isolated nucleic acid which specifically hybridizes to SEQ ID NO: 2 under stringent wash conditions of 0.2×SSc at 65° C. for 15 minutes and encodes an antifreeze protein having a thermal hysteresis activity greater than about 1.5° C. at about 1 mg/mL.

7. An isolated nucleic acid which specifically hybridizes under stringent wash conditions to the subsequence of SEQ ID NO:12 from nucleotides 105 to 359, wherein the nucleic acid encodes a thermal hysteresis protein that lacks a signal sequence.

8. The isolated nucleic acid of claim 7, wherein the nucleic acid specifically hybridizes under highly stringent wash conditions.

9. The isolated nucleic acid of claim 7 which encodes the 12 amino acid motif of SEQ ID NO:1.

10. An expression vector comprising the isolated nucleic acid of claim 1 operably linked to a promoter.

11. The expression vector of claim 10, wherein the promoter is heterologous.

12. The expression vector of claim 11, wherein the promoter is constitutive.

13. A cell into which, or into an ancestor of which, the isolated nucleic acid of claim 1 has been introduced.

14. The cell of claim 13, wherein the isolated nucleic acid sequence is translated into an antifreeze protein which is expressed externally from the cell.

15. The cell of claim 13, wherein said cell is a fungus.

16. The cell of claim 15, wherein the fungus is a yeast.

17. The cell of claim 16, wherein the yeast is selected from the group consisting of *Torulopsis holmil, Saccharomyces fragilis, Saccharomyces cerevisiae, Saccharomyces lactis*, and *Candida pseudotropicalis.*

18. The cell of claim 13, wherein the cell is a bacterium.

19. The cell of claim 18, wherein the bacterium is selected from the group consisting of *Streptococcus cremoris, Streptococcus lactis, Streptococcus thermophilus, Leuconostoc citrovorum, Leuconostoc mesenteroides, Lactobacillus acidophilus, Lactobacillus lactis, Bifidobacterium bifidum, Bifidobacterium breve*, and *Bifidobacterium longum.*

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